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Comparison of dissolution testing methods for the 25 mg dapivirine vaginal ring

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Key points

1 *In vitro* release testing of vaginal rings – including the 25 mg dapivirine ring – has historically been performed using non-compendial shaking incubator methods. Here, we tested *in vitro* release of the 25 mg dapivirine ring using an Apparatus 2 Rotating Paddle dissolution apparatus method, commonly used for compendial dissolution testing of oral dosage forms.

2 Significant loss of release medium due to evaporation was observed with the rotating paddle method. By accurately compensating for volume loss, dapivirine release profiles for the 25 mg rings were similar for the rotating paddle and shaking incubator methods.

3 The historical shaking incubator method for *in vitro* release testing of the 25 mg dapivirine vaginal ring offers increased practicality and reproducibility compared with the USP rotating paddle method. The rotating paddle method suffers significant evaporative loss of the release medium, which needs to be accounted for in order to accurately determine release values.

Background

There is a long history of using non-compendial, methods for *in vitro* release testing of vaginal rings. Typically, individual rings in a sealed glass flask containing a defined volume of release medium are placed in a temperature-controlled shaking incubator. Flasks are regularly and periodically sampled (usually with complete medium replacement) over weeks or months. The benefits of this method include a facile experimental set-up, no concerns over evaporation of the release media due to use of a sealed flask, easy sampling and media replacement procedures, and accurate control of temperature and rotational speed. This method also allows use of relatively large volumes of release media which may be necessary to maintain sink conditions throughout the experiment.

Objectives

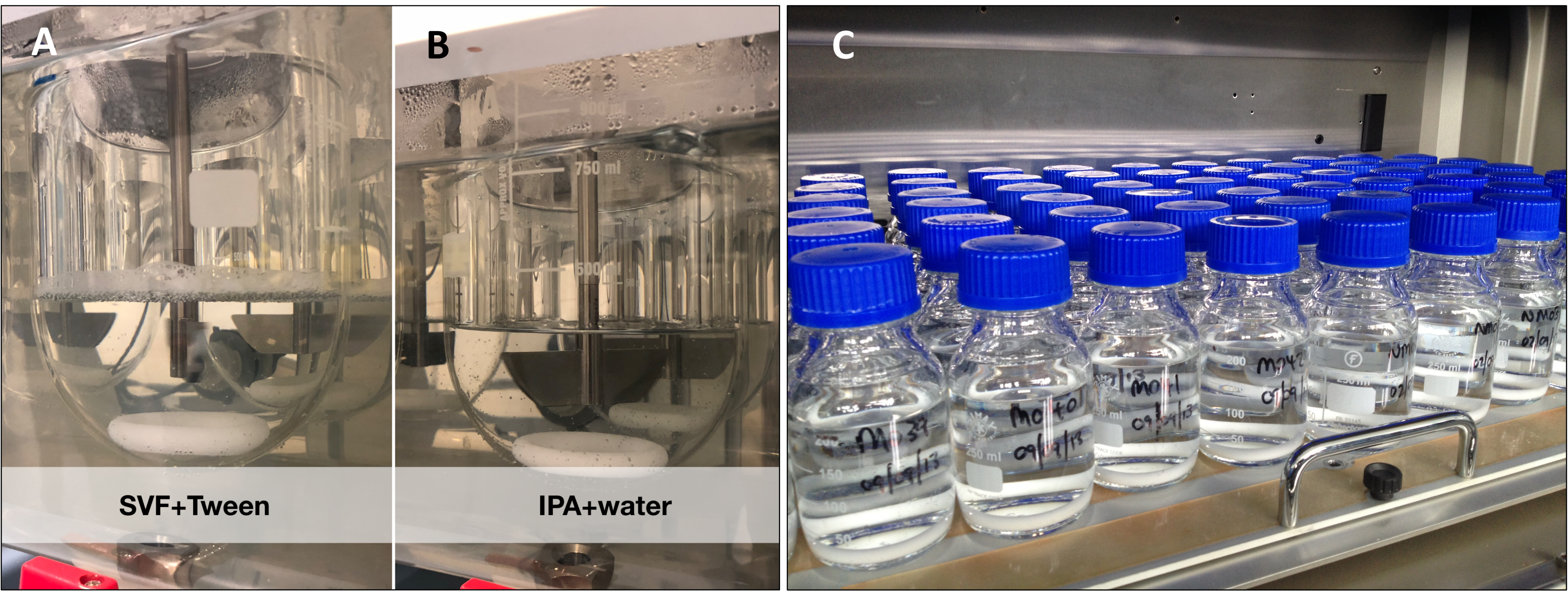
Here, we investigate use of a rotating paddle type dissolution apparatus for *in vitro* release testing of rings. Specifically, the objectives of the study were:

- To assess *in vitro* release of 25 mg dapivirine (DPV) ring into two common release media – isopropanol (IPA)+water and simulated vaginal fluid modified with 0.2% w/v Tween 80 (SVF+Tween) – using an Apparatus 2 Rotating Paddle dissolution apparatus (37 °C / 50 rpm / 300 mL medium) (Figs. 1A & 1B)
- To assess *in vitro* release of the 25 mg DPV ring into IPA+water and SVF+Tween – using the shaking incubator method (37 °C / 60 rpm / 100 or 200 mL medium) (Fig. 1C)
- To compare the release data obtained with the two methods

Methods

- 25 mg DPV, matrix-type, silicone elastomer vaginal rings were supplied by QPharma (Malmö, Sweden).
- Rotating paddle dissolution testing in both IPA+water (1:1 v/v; 300 mL) and SVF+Tween (300 mL) was performed using a ERWEKA DT 126 Light Dissolution Tester (50 rpm, 37°C).
- Shaking incubator dissolution testing of the rings was also performed, as described in the literature (100/200 mL, 37°C, 25 mm orbital diameter).
- DPV concentrations were quantified by HPLC.

Results & Discussion



Daily and cumulative release vs. time profiles for 25 mg DPV rings into IPA+water and SVF+Tween are presented in Fig. 2, for both the rotating paddle method – with and without adjustment for volume loss associated with evaporation of the release medium – and the shaking incubator method. Summary release data is presented in Table 1. Release into IPA+water was greater compared with release into SVF+Tween, reflecting differences in the solvating power of the media. Loss of release medium caused by evaporation was a serious issue with the rotating paddle method, particularly for the IPA+water medium. Approx. 26 mL/day (8.6% of the total volume) of the IPA+water release was lost to evaporation, compared with ~6 mL/day (2% of the total volume) for the SVF+Tween medium. By accurately measuring the volume of medium remaining in the flasks at each sampling timepoint, compensation for volume loss could be made such that release closely matched that measured using the shaking incubator method (Fig. 2, Table 1). However, having to compensate for volume loss at each sampling timepoint significantly reduces the practicality of the rotating paddle method. Impracticalities aside, the two methods produce similar *in vitro* release profiles.

Fig. 1. Apparatus 2 rotating paddle dissolution apparatus containing 25 mg DPV ring in 300 mL SVF+Tween (A) and IPA+water (B). C – Shaking incubator method for *in vitro* release testing of 25 mg DPV rings.

Fig. 2: 28-day *in vitro* DPV release profiles for 25 mg DPV vaginal rings. A – daily release into IPA+water; B – cumulative release into IPA+water; C – daily release into SVF+Tween; D – cumulative release into SVF+Tween.

■ Rotating paddle method: No adjustment for volume loss
□ Rotating paddle method: Adjustment for volume loss
○ Shaking incubator method

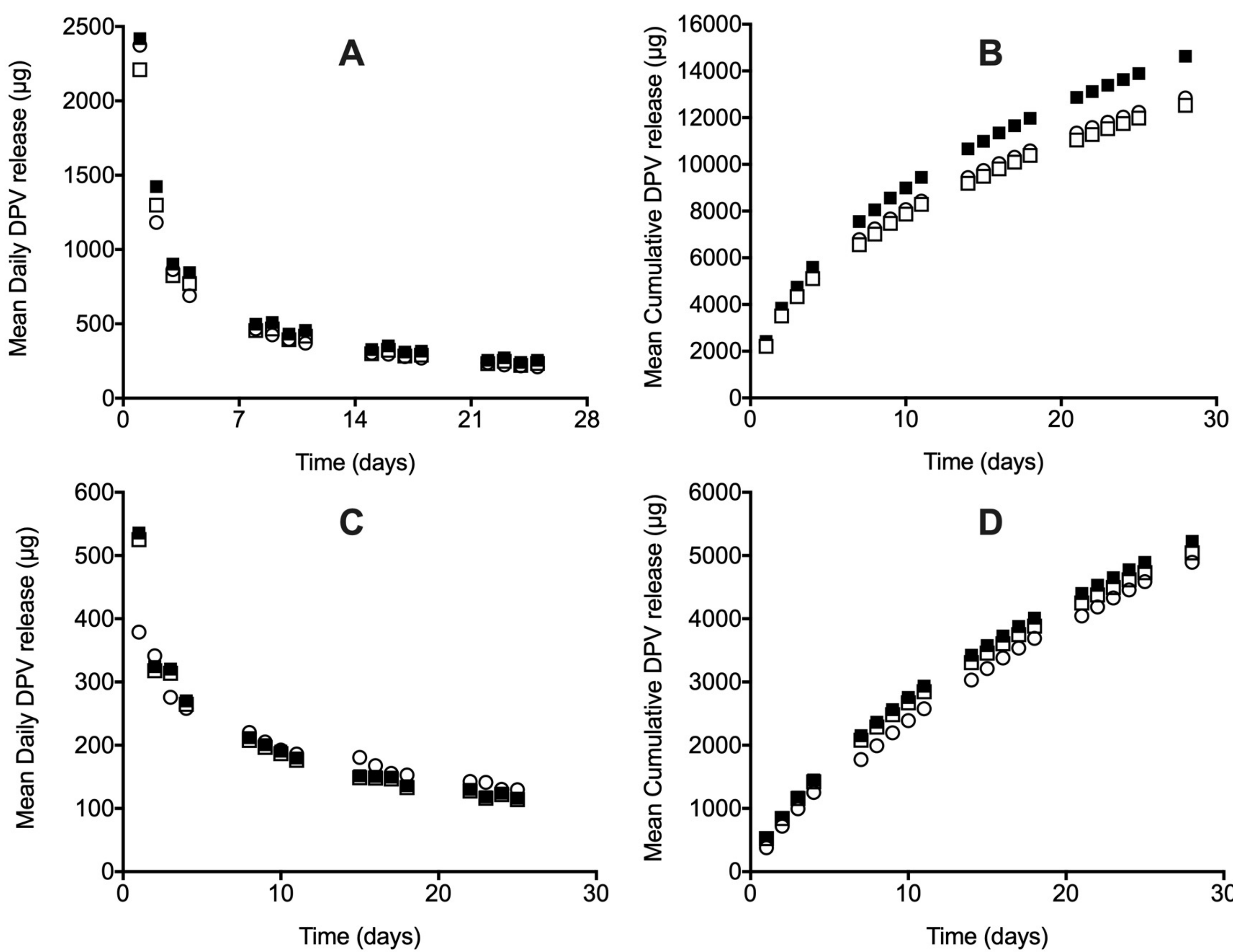


Table 1. Comparison of mean release rates and correlation coefficients (cumulative release vs. root time) for 25 mg DPV ring into IPA+water and SVF+Tween using USP Apparatus 2 (rotating paddle (RP), with and without adjustment for volume loss) and shaking incubator (SI) method.

Test method	Release medium	Volume adjust?	Mean release rate (µg/day ^{1/2})	r ² value
RP	IPA+water	No	2823	0.9983
RP	IPA+water	Yes	2369	0.9977
SI	IPA+water	–	2423	0.9982
RP	SVF+Tween	No	1121	0.9987
RP	SVF+Tween	Yes	1080	0.9988
SI	SVF+Tween	–	1082	0.9947